# Medication Adherence Affects Treatment Modifications in Patients With Type 2 Diabetes

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## ABSTRACT

**Background:** Low rates of treatment modification in patients with insufficiently controlled risk factors are common in type 2 diabetes. Although adherence problems are often mentioned in surveys as a reason for not intensifying treatment, observational studies have shown inconclusive results.

**Objective:** To assess how medication adherence affects treatment modifications for hypertension and hyperglycemia in patients with type 2 diabetes.

**Methods:** This was a cohort study of 11,268 primary care patients with type 2 diabetes in the Netherlands. Inclusion criteria were diagnosis before 2007, ≥1 prescription to antihypertensive or glucose-regulating medication in the preceding 6 months, and a systolic blood pressure level ≥140 mm Hg or glycosylated hemoglobin ≥7% in 2007. Patients on maximal treatment were excluded. Treatment modifications as observed from prescriptions were classified as none, dose increase, dose decrease, class switch, class addition, or class discontinuation. Refill adherence was assessed as medication possession ratio or length of last gap between refills. We performed multilevel multinomial regression analysis to test for associations.

**Results:** We included 4980 diabetic patients with elevated blood pressure and 2945 diabetic patients with elevated glycosylated hemoglobin levels. Patients with lower adherence for antihypertensive drugs were more likely to have those medications discontinued (odds ratio [OR] for every 10% lower medication possession ratio =1.22; 95% CI, 1.11–1.33) or the dose decreased (OR = 1.14; CI 1.01–1.28). For glucose-regulating medication, dose increases (OR = 0.92; 95% CI, 0.85–0.98) and medication additions (OR = 0.90; 95% CI, 0.82–0.99) were less likely in patients with lower adherence levels.

**Conclusions:** Low adherence inhibits the intensification of glucose-regulating but not antihypertensive medication in type 2 diabetic patients with insufficiently controlled risk factors in the Netherlands. Adherence problems may lead to diminished or even discontinued antihypertensive treatment. (*Clin Ther.* 2011;33:121–134) © 2011 Elsevier HS Journals, Inc.

**Key words:** hyperglycemia, hypertension, medication adherence, primary care, therapy modification, type 2 diabetes.

## INTRODUCTION

Despite considerable progress in the field of hypertension and other cardiovascular risk factor management during the last decade, undertreatment remains a topic of importance, especially in high-risk populations such as patients with type 2 diabetes.[1–4] Both poor adherence and lack of treatment intensification seem common in diabetic patients not reaching target risk factor levels.[5] Several studies have looked into reasons for physicians not acting when confronted with patients

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with elevated risk factor levels.[6–12] Physicians may be reluctant to intensify pharmacotherapy when patients already take multiple medications,[6] when patients have difficulty with lifestyle modifications,[7] or when patients are reluctant to take medication.[8] Perception of poor adherence has often been mentioned in surveys by physicians as a reason not to intensify treatment.[5,10,11] Observational studies, however, have reported conflicting results on the association between medication adherence and treatment intensification.[13–17] Both negative and positive associations have been observed between suboptimal adherence and treatment modifications,[13,14,17] whereas no such associations were found in other studies.[15,16]

Some disagreements in these observational studies may be due to the differences in definitions of both medication adherence and treatment intensification. Medication adherence has been assessed using various measures based on prescription refill data.[18–20] This often leads to a binary classification between patients collecting sufficient amounts of pills or prescription refills and those collecting inadequate numbers of pills or having large gaps between refills. Treatment intensification is also commonly assessed as a binary outcome (intensification or not), including sometimes only dose increase or addition of a new drug as intensification[13–15] and sometimes switches within or between classes of drugs.[16,17] All other therapy modifications are classified as no intensification, leading to inconsistent definitions of what is considered to be no treatment intensification.

Aside from these inconsistencies, binary definitions of therapy modifications can obscure meaningful associations. In patients with adherence problems, it is usually appropriate not to intensify therapy; therefore, testing is performed to determine whether low adherence levels are associated with no intensification. Specific therapy modifications, however, may be appropriate, depending on the underlying reasons for nonadherence. For instance, when patients are nonadherent because of perceived side effects, switching to another drug class or decreasing the medication dose may be warranted instead of not intensifying treatment. To our knowledge there are no studies on the association between medication adherence and distinct therapy modifications, separating intensifications from switches, dose changes, discontinuation, or no change in medication.

The aim of this study was to assess how patients' medication adherence affects distinct prescribing modifications for hypertension and hyperglycemia in type 2 diabetic patients in the Netherlands. For this, we include different continuous and binary adherence estimates.

## PATIENTS AND METHODS

We conducted a cohort study to assess the influence of medication adherence on prescribing modifications for hypertension and hyperglycemia in patients with type 2 diabetes in the Netherlands. Clinical measurements, prescriptions, and demographic data for patients with type 2 diabetes were collected from the Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) database. We used data from 2007, which was the most recent year with complete follow-up available. This Dutch database contains anonymized longitudinal information retrieved from electronic medical records of general practitioners (GPs).[21] In the Netherlands, patients are registered with a single GP. The GPs in our study prescribe electronically, ensuring full information on prescribed drugs and dosing schemes. Having electronic medical records allows the GPs to view recent prescribing history, a minimal prerequisite for detecting possible adherence issues. Ethics committee approval was not required because research using anonymous medical records in the Netherlands does not warrant it.[22]

### Study Population

The study population consisted of patients with a diagnosis of type 2 diabetes who were managed by 142 GPs. Patients were included if they were diagnosed before the year 2007, had ≥1 risk factor measurement above the treatment target (≥140 mm Hg for systolic blood pressure; ≥7% for glycosylated hemoglobin [$HbA_{1c}$]) in 2007, and received ≥1prescription for an antihypertensive or glucose-regulating drug in the preceding 6 months. Because our data do not allow for assessing referrals to specialist care nor changes in insulin dose, we excluded patients from the analyses if they had already received ≥3 drug classes on maximal maintenance dose for blood pressure lowering or if they had been prescribed insulin as glucose-regulating medication (see **Table 1** for definitions).

Table I. Medication definitions used.

| | |
|---|---|
| Antihypertensive drug classes | Renin-angiotensin-aldosterone system inhibitors; diuretics; β- blockers; calcium channel blockers; centrally acting antihypertensives |
| Glucose-regulating drug classes | Metformin; sulfonylureas; acarbose; thiazolidinediones; other oral drugs (repaglinide, exenatide) |
| Maximal treatment | For glucose-regulating medication, prescription of insulin was defined as having reached maximal medication; for blood pressure-lowering medication, 3 or more drug classes prescribed at maximum maintenance dose was defined as maximal treatment |
| Dose increase | Increase of the prescribed daily dose of a drug |
| Dose decrease | Decrease of the prescribed daily dose of a drug |
| Start | Prescription of a class not previously prescribed within a 270-day* period |
| Discontinuation | Prescription of a class not prescribed within a 270-day* period since the date of the last prescription. To estimate the date of the discontinuation we used the date of a coinciding event: a dose increase or decrease of another drug or addition of a new class that occurred during the course of the last prescription. In cases of no coinciding event, we used the calculated end date of the last prescription. A discontinuation occurring before the index date counted as a class discontinuation if the derived discontinuation date was within 7 days of the index date |
| Switch | A class was discontinued (see above) and a new class started within 7 days of the discontinuation date |
| Addition | A new class started without another class being discontinued within 7 days of the start date |

* 270 days corresponds with 3 times the maximal duration of a prescription for chronic drug use in the Netherlands.

### Treatment Modifications

For each patient, the first elevated risk factor observation in 2007 was taken as the index observation. The primary outcome in our study was the first therapy modification after the index observation. Therapy modifications were assessed during a 60-day period starting on the index date. Modifications as observed from prescriptions were classified as follows: none, dose increase, dose decrease, class switch, addition of a new class, and discontinuation of a class (see **Table 1** for definitions). For glucose-regulating medication, we included start of insulin as a distinct treatment modification. In the case of multiple therapy intensifications, we classified insulin start as predominant over other intensifications and class addition as predominant over dose increase. In the case of multiple reductions, we classified class discontinuation as predominant over dose decrease.

Patients with opposing modifications (n = 17) were excluded (eg, a dose increase coinciding with a dose decrease). Patients who left the practice within 270 days from the index observation were excluded, owing to insufficient follow-up. For comparison, we also constructed the commonly used binary outcome: 1) intensification (ie, dose increase or addition of class), or 2) no intensification (all other cases).

### Medication Adherence

Medication adherence was assessed at the drug class level using prescription refill data in the 1-year period before the index date. Drug classes signify groups or single drugs that can be expected being prescribed concurrently (**Table 1**). Within a drug class, on the other hand, drugs are expected to be prescribed sequentially. The algorithm used to calculate the adherence parameters corrects for overlapping prescriptions, dose

changes, and drug and class switches. Details on this algorithm are available in **Appendix I**.

We calculated 2 common adherence measures: the first expresses the length of the most recent gap between 2 prescriptions (period without medication); the second calculates the overall medication possession ratio (MPR) up to the index date.[19,23] The MPR assesses the number of days a drug is prescribed in relation to the prescribing period and is a measure of overall medication availability. The length of the most recent gap may be more visible to prescribing physicians than a period assessment like the MPR. The MPR, however, may better reflect chronic suboptimal adherence. We quantified adherence using the largest last gap in any of the concurrently prescribed drug classes within either antihypertensive or glucose-regulating medication and, analogously, used the lowest MPR within each therapeutic group.

### Statistical Analysis

To analyze the association between adherence and treatment modification, we calculated adjusted odds ratios (OR) and their 95% CI using multilevel multinomial logistic regression with Stata version 11 (StataCorp LP, College Station, Texas), correcting for clustering at the GP level. Associations were considered significant when the 95% CI did not include the value of 1.0. Potential confounders added to the models were the level of the index observation for $HbA_{1c}$ and systolic blood pressure, age, sex, diabetes duration (as provided by the GP), number of risk factor–specific drug classes used, and number of other chronic drugs used. In prescribing glucose-regulating medication it is recommended to increase a drug's dose until its maximal dose is reached[24]; therefore, we included a binary variable to indicate whether all drugs used were described at maximal maintenance dose or not.

To assess the effect of using different adherence and outcome measures, all analyses were conducted using either the last gap or the MPR as continuous adherence measures and using distinct treatment modifications as well as the binary intensification outcome.

An OR was presented for every 10% decrease in MPR or every 14-day increase of last gap length, both representing lower adherence levels. In additional analyses, we used categorical instead of continuous adherence measures based on commonly used end points of 15 and 30 days for gap length and of 70% and 80% for MPR level.

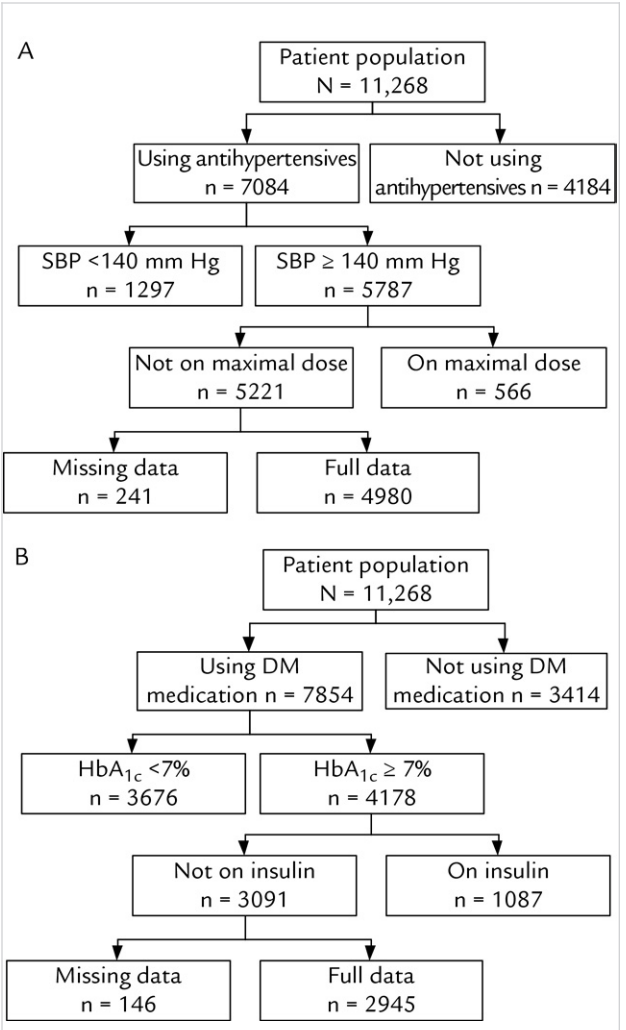


Figure 1. Patient selection for antihypertensive (A) and glucose-regulating (B) medication. SBP = systolic blood pressure; DM = diabetes mellitus; $HbA_{1c}$ = glycosylated hemoglobin.

## RESULTS

Of the 11,268 primary care patients with type 2 diabetes, 4980 and 2945 were included in the analyses for antihypertensive and glucose-regulating medication, respectively (**Figure 1**). The patient populations differed slightly with respect to percentage female, age, and diabetes duration (**Table 2**).

The most frequently used antihypertensive drug classes were renin-angiotensin-aldosterone system inhibitors, diuretics, and β-blockers. One third of patients were on monotherapy, whereas 38% used 2 classes (**Table 2**). Most patients showed high adher-

Table II. Characteristics of patient population and medication use (numbers [%] presented, unless otherwise specified).

| | Antihypertensive | | Glucose Regulating | |
|---|---|---|---|---|
| No. of patients | 4980 | | 2945 | |
| Female | 2812 | (56.5) | 1483 | (50.4) |
| Systolic blood pressure, mean (SD) | 154.6 | (14.9) | | |
| $HbA_{1c}$, %, mean (SD) | | | 7.6 | (0.8) |
| Age, y, mean (SD) | 66.7 | (11.1) | 66.1 | (12.1) |
| Diabetes duration, y, mean (SD) | 6.0 | (5.7) | 5.7 | (5.2) |
| No. of other chronic drugs, median (IQR) | 4 | (3) | 4 | (4) |
| *Drug classes used prior to index date* | | | | |
| RAAS inhibitors | 3547 | (71%) | | |
| Diuretics | 2669 | (54%) | | |
| ß-blocking agents | 2306 | (46%) | | |
| Calcium channel blockers | 1054 | (21%) | | |
| Other antihypertensives | 87 | (2%) | | |
| Biguanides (ie, metformin) | | | 2324 | (79%) |
| Sulfonylureas | | | 2021 | (69%) |
| $\alpha$-Glucosidase inhibitors (ie, acarbose) | | | 12 | (0.4%) |
| Thiazolidinediones | | | 381 | (13%) |
| Other oral diabetes drugs | | | 2 | (0.1%) |
| *Number of drug classes used* | | | | |
| 1 class | 1675 | (33.6%) | 1339 | (45.5%) |
| 2 classes | 1913 | (38.4%) | 1417 | (48.1%) |
| ≥3 classes | 1392 | (28.0%) | 189 | (6.4%) |
| All drugs at maximal dose | 7 | (0.1%) | 219 | (7.4%) |
| *MPR classes* | | | | |
| <50% | 292 | (5.9%) | 107 | (3.6%) |
| ≥50 to <70% | 304 | (6.1%) | 219 | (7.4%) |
| ≥70 to <80% | 314 | (6.3%) | 249 | (8.5%) |
| ≥80% | 4070 | (81.7%) | 2370 | (80.5%) |
| *Last gap length classes* | | | | |
| <15 days | 3761 | (75.5%) | 2424 | (82.3%) |
| ≥15 to <30 days | 519 | (10.4%) | 239 | (8.1%) |
| ≥30 days | 700 | (14.1%) | 282 | (9.6%) |
| *Number of drug classes with lowest MPR* | | | | |
| 1 class | 3844 | (77.2%) | 2523 | (85.7%) |
| 2 classes | 867 | (17.4%) | 391 | (13.3%) |
| ≥3 classes | 269 | (5.4%) | 31 | (1.1%) |
| *Number of drug classes with largest last gap* | | | | |
| 1 class | 3673 | (73.8%) | 2130 | (72.3%) |
| 2 classes | 986 | (19.8%) | 742 | (25.2%) |
| ≥3 classes | 321 | (6.4%) | 73 | (2.5%) |

$HbA_{1c}$ = glycosylated hemoglobin; IQR = interquartile range; MPR = medication possession ratio; RAAS = renin-angiotensin-aldosterone.

Table III. First therapy modifications within 60 days after the elevated risk factor observation (index date).

| | Antihypertensive | | Glucose Regulating | |
|---|---|---|---|---|
| Modification | n | % | n | % |
| None | 4301 | 86.4 | 2030 | 68.9 |
| Increase | 144 | 2.9 | 506 | 17.2 |
| Decrease | 65 | 1.3 | 71 | 2.4 |
| Switch | 14 | 0.3 | 12 | 0.4 |
| Addition* | 370 | 7.4 | 234 | 8.0 |
| Discontinuation | 86 | 1.7 | 66 | 2.2 |
| Insulin start | — | — | 26 | 0.9 |
| Total | 4980 | | 2945 | |

* Additions by switching to a combination drug occurred in 17 cases with antihypertensive medication and in 4 cases with glucose-regulating medication.

ence to antihypertensive medication (≥80% MPR [82% of patients] or last gap length <15 days [76%]); low adherence was found in 6% (MPR <50%) to 14% (last gap length ≥30 days).

The most frequently used glucose-regulating drugs were metformin and sulfonylureas. Monotherapy was observed in 46% of patients, whereas 48% used 2 medication classes. In 81% of the patients, adherence was ≥80% MPR, whereas 83% had a last gap length <15 days. Only 4% had an MPR below 50%, whereas 10% had a last gap length of ≥30 days.

In patients using multiple drugs for the same indication, suboptimal adherence was mostly limited to a single drug class. Of patients with adherence levels of MPR <80% or last gap ≥15 days using ≥2 drugs, between 89% and 96% of the adherence problem occurred in a single drug class.

In 86% of patients using antihypertensive medication and 69% of those using glucose-regulating medication, no therapy modification was observed within the 60-day period following the elevated risk factor level (Table 3). The most frequently observed modifications for antihypertensive and glucose-regulating medications were dose increase (2.9% and 17.2%, respectively) and addition of a new drug class (7.4% and 8.0%, respectively). The least frequent modification was a class switch. Half of the treatment modifications occurred within 14 and 17 days for antihypertensive and glucose-regulating medication, respectively.

### Antihypertensive Medication Treatment Modification

Patients with lower adherence, expressed as lower levels of MPR or higher levels of last gap, were more likely to have an antihypertensive drug class discontinued (Figure 2) (OR = 1.22, 95% CI, 1.11–1.33 for MPR [–10%]; OR = 1.11, 95% CI, 1.05–1.17 for last gap [+14 days]). The likelihood of a dose increase was not significantly lower in patients with lower adherence levels (CI intervals including 1.0). Only for the MPR measure were patients with lower adherence levels more likely to receive a dose decrease (OR =1.14, 95% CI, 1.01–1.28). When using the binary outcome of treatment intensification, we did not find significant associations with the adherence measures (OR = 1.04, 95% CI, 0.99–1.10 for MPR [–10%]; OR = 1.00, 95% CI, 0.97–1.04 for last gap [+14 days]).

### Glucose-Regulating Medication Treatment Modification

For glucose-regulating medication, we observed a lower likelihood for dose increases in patients with lower adherence levels using either adherence measure (Figure 2) (OR = 0.92, 95% CI, 0.85–0.98 for MPR [–10%]; OR = 0.88, 95% CI, 0.81–0.96 for last gap [+14 days]). Only for the MPR measure did we find a lower likelihood for an addition of a new class in patients with lower adherence levels (Figure 2) (OR = 0.90, 95% CI, 0.82–0.99). The level of adherence did

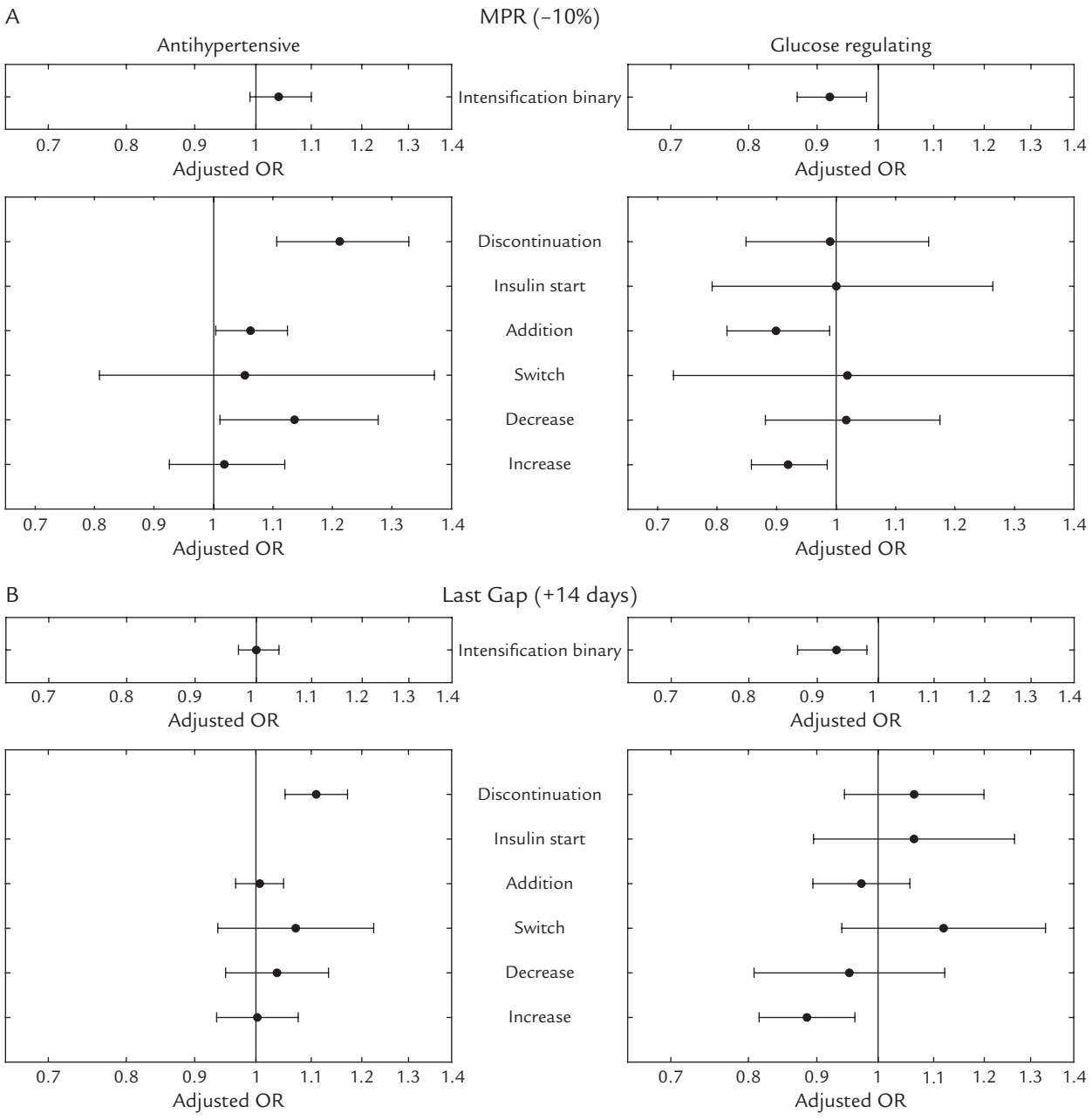


Figure 2. The influence of medication adherence expressed as (A) medication possession ratio (MPR, 10% decrease) and (B) length of last gap (14 days increase) on binary (top) and multinomial (bottom) therapy modifications for antihypertensive medication (left) and oral glucose-regulating medication (right). Presented are odds ratios (OR) adjusted for risk factor level, age, sex, diabetes duration, number of risk factor–specific drug classes used, number of other chronic drugs used, and maximal dosing for glucose-regulating medication. Error bars indicate 95% CI.

not significantly affect starting with insulin. The binary outcome of intensification also showed that a lower level of adherence was associated with a lower probability to intensify treatment (OR = 0.92, 95% CI, 0.87–0.98 for MPR [–10%]; OR = 0.93, 95% CI, 0.87–0.98 for last gap [+14 days]).

### Categorical Adherence Measures

For several associations significance was lost when using categorical adherence measures. For antihypertensive medication, only the association between the MPR measures and dose decrease (OR = 2.23, 95% CI, 1.23–4.03 for MPR [<70%]) or drug class discontinuation (OR = 2.37, 95% CI, 1.42–3.94 for MPR [<70%]) remained significant, whereas those for the categorical last gap measures did not (**Appendix II**, CI including 1.0). For glucose-regulating drugs, the associations with class addition and dose increase were lost in the cases of categorical MPR and last gap (≥30 days) measure (**Appendix II**, CI including 1.0).

## DISCUSSION

In patients with a low adherence to antihypertensive drugs, we observed a higher likelihood to discontinue the antihypertensive drug treatment. This result was in contrast to glucose-regulating medication in which a lower adherence was associated with fewer dose increases and fewer additions of a new drug class, indicating the expected reaction of not intensifying treatment in case of observed low adherence.

The negative association between suboptimal adherence and treatment intensification may thus depend more on the therapeutic area than on the definitions of adherence or treatment intensification. The effect seen for glucose-regulating medication was consistent for the different definitions. Physicians appear to take adherence into account when confronted with insufficient glycemic control by not intensifying the glucose-regulating treatment in patients with low adherence levels.[13] For antihypertensive treatment; however, we found no such association. This result is consistent with findings of other studies focussing on antihypertensive treatment.[14,16] This dissimilar finding between the 2 therapeutic areas can be caused by differences in attention given to adherence but also by reasons underlying adherence and related possible reactions to nonadherence at physician and patient level.

In previous studies, we have found indications for a glucose-centered approach to diabetes risk factor management,[1,25] which also has been reported by other investigators.[26,27] Such a management strategy may lead to more attention and, thereby, higher awareness of adherence problems for glucose-regulating medication. In addition, the link between suboptimal adherence and risk factor levels may be less clear for blood pressure than for $HbA_{1c}$.[13] This can further diminish the physicians' awareness of the underlying cause of suboptimal blood pressure control. However, even when the physician is aware of a potential adherence problem, differences in patients' reactions also can explain the differences in observed treatment modifications. Self-reported adherence of patients was found to be higher with antihypertensive than glucose-regulating medication,[28] whereas refill rates have shown the opposite results.[29,30] These findings imply that patients either overestimate adherence or are more reluctant to admit adherence problems with antihypertensive medication than glucose-regulating medication. All these factors contribute to the pattern we observed, where physicians intensify antihypertensive treatment regardless of low medication adherence levels.

We did observe other treatment modifications in patients with low adherence to antihypertensive medication. Such patients had a higher probability to discontinue a drug class. This finding of poor adherence to antihypertensive drugs being a strong predictor of discontinuation has been observed before,[31] which may indicate a patient-driven pattern of nonadherence rather than a decision of the physician to modify the treatment. Patients with low adherence to antihypertensive drugs, however, tended to receive more dose decreases and more additions of a new drug class, which are treatment modifications made by physicians. A pharmacy database study in the Netherlands, which focused on first-time users of antihypertensive drugs, found a similar association.[17] This finding may be explained by reactions to perceived adverse effects underlying suboptimal adherence. Especially for antihypertensive treatment, there are usually many options to decrease the dose of one drug while adding another drug in order to increase effectiveness and reduce adverse effects.

The real barrier to better risk factor control may not be addressed if treatment is intensified despite low adherence.[14,32] Physicians may have trouble detecting nonadherence in daily practice. There is a need for better detection and visibility of adherence,[16,33] because correctly distinguishing nonresponse to therapy from nonadherence is important. Currently, the GP systems do not provide active feedback regarding possible adherence problems. Such tools, however, could be implemented easily in the medical record systems when physicians prescribe electronically. In our study, the choice of the

adherence measure affected our results to some extent. The MPR, which is an overall period adherence estimate, was more strongly related with treatment modifications than an adherence measure based on the last gap between prescription refills. It is possible, therefore, that the MPR better reflects adherence judgments made by physicians.

When looking at treatment modification as a binary outcome, some interesting findings are lost. Although the conclusions are similar regarding the associations between adherence and distinct intensifications for glucose-regulating medication (ie, less intensification in patients with lower adherence levels), they are different for antihypertensive medication. Using a binary outcome, one may conclude that there is no association between adherence and treatment changes, whereas our study showed that adherence levels are associated with specific treatment modifications, such as discontinuation, dose decrease, and addition of a new drug class. Such modifications could be considered appropriate action in patients not adherent to treatment when they have experienced adverse effects. Also, by classifying various modifications in the binary outcome as "no intensification," one could erroneously observe a negative association between adherence and intensification.

Types and number of drugs used in our study population are comparable to those reported elsewhere.[16,34–36] Using the common cutoff point for adherence (≥80% MPR), the level of adherence observed in our study population is comparable to some other studies' findings,[5,30] although much lower levels also have been reported.[16,18] These differences could be caused by differences in the health care system and reimbursement, patient population, and data source used. We used electronic prescribing data, whereas others have used dispensing data or claims databases.[5,16,30] Although these sources are all related, lower adherence levels may be observed using dispensing data.[33] When we compare the results obtained from the categorical adherence measures to the results from the continuous ones, we see that we lose considerable power to detect associations, which can be attributable to a lower precision of estimates and to the (arbitrary) choice of the cutoff points. Therefore, as has been recommended before,[18] it is better to use continuous measures in studies of adherence.

### Strengths and Limitations

We used longitudinal information retrieved from electronic medical records of GPs. This approach has both advantages and disadvantages. The detailed longitudinal dataset enabled us to consider the first treatment modification within 60 days after an elevated risk factor observation, which is in contrast to other studies that looked at treatment intensifications occurring in longer periods irrespective of whether other modifications preceded these.[5,13,15,17] Using a short period makes it more likely that the treatment modification is indeed a reaction to the observed elevated risk factor level. The obvious limitation is that we were unable to assess which other actions may have been taken to improve medication adherence or who took the initiative to discontinue the medication. It is possible that in some cases the GPs decided to improve adherence by educating and motivating the patient as well as increase treatment at the same time. This type of action, however, has the risk of predisposing patients to overtreatment.

Patient and disease complexity could confound the associations between adherence and treatment intensification. Although we corrected for proxies of this (diabetes duration, age, and polypharmacy) in our analyses, residual confounding cannot be excluded.

Using prescription refill data for calculating adherence has the disadvantage of overestimating actual adherence, because patients may collect their prescriptions and not actually take the medication. On the other hand, although these data do not reflect "true" medication adherence, they reflect prescription refill adherence as can be observed by the GPs from their records. In addition, using prescription data from electronic medical records has the advantage of having a direct measure of the treatment modifications made by the GPs. Our data did not allow for correcting medication use for periods of inpatient hospitalization. Although such periods do not necessarily result in gaps in home medication use, because patients sometimes use their home medication in the hospital, this limitation may have resulted in underestimation of patients' adherence levels.

Finally, there is no best method for measuring adherence using prescription data,[19,23] which is why we chose to use 2 different adherence measures. There is also no consensus on how to calculate adherence in patients using multiple drugs for the same indication.[37]

We focused on the drug with the poorest adherence, because we expect this to be relevant information for the prescriber, and patients using multiple drugs can show poor adherence on a single drug.[29] Our results confirm that in patients on multitherapy poor adherence occurs predominantly in a single drug class. By averaging adherence measures over concurrently used drugs, the power to assess an association with nonadherence to a single drug is decreased.

## CONCLUSIONS

This study demonstrates that low adherence to glucose-regulating drugs does reduce the chance of intensifying such treatment in insufficiently controlled patients with type 2 diabetes in the Netherlands. This did not occur for antihypertensive treatment, indicating that adherence problems cannot explain the lack of antihypertensive treatment intensification in these patients. Low adherence may lead to other treatment modifications, which are overlooked when focusing only on whether the treatment is intensified. Our data suggest that this is the case for antihypertensive medication, where low adherence may lead to diminishing or the discontinuation of such treatment in patients with type 2 diabetes.

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Appendix I. Prescriptions (Rx) preprocessing.

| | |
|---|---|
| Period definition | All Rx of the therapeutic class prescribed in study period ± 270 days |
| Correct erroneous Rx | Exclude Rx with calculated duration <2 days |
| Correct concomitant use of same drug | Sum daily use within first Rx and set to longest duration and delete the second |
| Correct stockpiled Rx | Exclude second Rx if gap following Rx is <80% of the summed calculated duration |
| Correct isolated short Rx | Exclude Rx with calculated duration <15 days and not repeated within 7 days |
| Correct for daily use change | Change in daily use within a single ATC results in correction of Rx duration |
| Correct switch to/from combination | Correct Rx duration |
| Correct variations in Rx collection at ATC level | Line up at ATC level |
| Correct switch to other drug | Correct Rx duration in case of switch to another ATC |
| Correct variations in Rx | Line up |
| Correct class switch | Adjust period end in case of a switch to another therapeutic class |
| Correct class start | Adjust period start in case of a class start |

ATC = Lowest level of the Anatomical Therapeutic Chemical classification.

Appendix II. Model results for continuous and categorical adherence assessments for distinct therapy modifications.

| | Antihypertensive (n = 4980) | | | Glucose Regulating (n = 2945) | | |
|---|---|---|---|---|---|---|
| | OR* | 95% CI | | OR* | 95% CI | |
| Intensification (binary) | | | | | | |
| MPR (−10%) | 1.04 | 0.99 | 1.10 | **0.92** | 0.87 | 0.98 |
| Last gap (+14 days) | 1.00 | 0.97 | 1.04 | **0.93** | 0.87 | 0.98 |
| MPR < 80% | 1.02 | 0.80 | 1.31 | **0.75** | 0.59 | 0.94 |
| MPR < 70% | 1.17 | 0.89 | 1.55 | 0.77 | 0.58 | 1.02 |
| Last gap ≥ 30 days | 1.04 | 0.79 | 1.36 | **0.56** | 0.40 | 0.77 |
| Last gap ≥ 15 days | 1.07 | 0.86 | 1.33 | **0.59** | 0.46 | 0.76 |
| Increase | | | | | | |
| MPR (−10%) | 1.02 | 0.93 | 1.12 | **0.92** | 0.85 | 0.98 |
| Last gap (+14 days) | 1.00 | 0.93 | 1.08 | **0.88** | 0.81 | 0.96 |
| MPR < 80% | 0.86 | 0.54 | 1.35 | 0.78 | 0.60 | 1.01 |
| MPR < 70% | 1.02 | 0.61 | 1.71 | 0.76 | 0.54 | 1.06 |
| Last gap ≥ 30 days | 0.67 | 0.38 | 1.19 | **0.53** | 0.36 | 0.79 |
| Last gap ≥ 15 days | 0.93 | 0.63 | 1.38 | **0.63** | 0.47 | 0.84 |
| Decrease | | | | | | |
| MPR (−10%) | **1.14** | 1.01 | 1.28 | 1.02 | 0.88 | 1.18 |
| Last gap (+14 days) | 1.04 | 0.95 | 1.13 | 0.95 | 0.81 | 1.12 |
| MPR < 80% | **1.78** | 1.03 | 3.08 | 1.33 | 0.77 | 2.29 |
| MPR < 70% | **2.23** | 1.23 | 4.03 | 1.16 | 0.58 | 2.32 |
| Last gap ≥ 30 days | 1.40 | 0.74 | 2.64 | 1.07 | 0.50 | 2.28 |
| Last gap ≥ 15 days | 1.33 | 0.78 | 2.28 | 1.02 | 0.55 | 1.86 |
| Switch | | | | | | |
| MPR (−10%) | 1.05 | 0.81 | 1.37 | 1.02 | 0.72 | 1.43 |
| Last gap (+14 days) | 1.07 | 0.94 | 1.22 | 1.12 | 0.94 | 1.33 |
| MPR < 80% | 1.15 | 0.32 | 4.20 | 1.23 | 0.33 | 4.62 |
| MPR < 70% | 1.86 | 0.51 | 6.79 | 1.38 | 0.30 | 6.45 |
| Last gap ≥ 30 days | 1.64 | 0.45 | 5.92 | 2.75 | 0.72 | 10.45 |
| Last gap ≥ 15 days | 1.23 | 0.38 | 3.95 | 3.06 | 0.95 | 9.88 |
| Addition | | | | | | |
| MPR (−10%) | 1.06 | 1.00 | 1.12 | **0.90** | 0.82 | 0.99 |
| Last gap (+14 days) | 1.01 | 0.97 | 1.05 | 0.97 | 0.89 | 1.06 |
| MPR < 80% | 1.15 | 0.87 | 1.52 | 0.68 | 0.46 | 1.01 |
| MPR < 70% | 1.31 | 0.96 | 1.80 | 0.74 | 0.46 | 1.19 |
| Last gap ≥ 30 days | 1.20 | 0.89 | 1.62 | 0.62 | 0.37 | 1.05 |
| Last gap ≥ 15 days | 1.13 | 0.88 | 1.45 | **0.53** | 0.35 | 0.82 |

Appendix II (continued).

| | Antihypertensive (n = 4980) | | | Glucose Regulating (n = 2945) | | |
|---|---|---|---|---|---|---|
| | OR* | 95% CI | | OR* | 95% CI | |
| Discontinuation | | | | | | |
| MPR (−10%) | **1.22** | 1.11 | 1.33 | 0.99 | 0.85 | 1.15 |
| Last gap (+14 days) | **1.11** | 1.05 | 1.17 | 1.06 | 0.94 | 1.20 |
| MPR < 80% | **2.44** | 1.55 | 3.84 | 0.87 | 0.47 | 1.61 |
| MPR < 70% | **2.37** | 1.42 | 3.94 | 1.01 | 0.48 | 2.11 |
| Last gap ≥ 30 days | 1.63 | 0.96 | 2.78 | 1.32 | 0.63 | 2.78 |
| Last gap ≥ 15 days | 1.22 | 0.76 | 1.97 | 1.03 | 0.55 | 1.94 |
| Insulin start | | | | | | |
| MPR (−10%) | | | | 1.00 | 0.79 | 1.27 |
| Last gap (+14 days) | | | | 1.06 | 0.89 | 1.26 |
| MPR < 80% | | | | 0.65 | 0.23 | 1.80 |
| MPR < 70% | | | | 0.73 | 0.21 | 2.53 |
| Last gap ≥ 30 days | | | | 0.80 | 0.22 | 2.86 |
| Last gap ≥ 15 days | | | | 0.59 | 0.19 | 1.78 |

MPR = medication possession ratio; OR = odds ratio.
* Boldface OR: $P < 0.05$.